EXTENDED REPORTS

Long term prognosis of reactive salmonella arthritis

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Abstract

***Objectives*—Reactive joint complications triggered by salmonella gastroenteritis are increasingly reported, but the outcome and long term prognosis of the patients is incompletely known. This study looked at the prognosis of salmonella arthritis in patients hospitalised in 1970–1986.**

***Methods*—Hospital records from two hospitals in southern Finland were screened for patients with the discharge diagnosis of salmonellosis or reactive, postinfectious arthritis or Reiter's disease. For the patients with confirmed diagnosis of reactive salmonella arthritis, data about the acute disease were collected from the hospital records. A follow up study was performed.**

***Results*—There were 63 patients (28 women, 35 men, mean age 36.5 years) with salmonella arthritis. Urethritis occurred in 27%, eye inflammation in 13%, and low back pain in 44% of the patients. HLA-B27 was present in 88%. More men than women were HLA-B27 positive. HLA-B27 positive patients had higher erythrocyte sedimentation rate (mean 80.9 *v* 46.5 mm 1st h, p = 0.0180). Also, extra-articular features and radiological sacroiliitis were seen only in HLA-B27 positive patients. A follow up study was performed on 50 patients mean 11.0 (range 5–22 years) later. Twenty patients had recovered completely. Ten patients had mild joint symptoms, 11 patients had had a new acute transient arthritis, and five acute iritis. Eight patients had developed chronic spondyloarthropathy. Radiological sacroiliitis was seen in six of 44 patients, more frequently in male than in female patients (32% *v* 0%; p = 0.0289). Recurrent or chronic arthritis, iritis or radiological sacroiliitis developed only in HLA-B27 positive patients.**

***Conclusion*—Joint symptoms are common after reactive salmonella arthritis. HLA-B27 contributes to the severity of acute disease and to the late prognosis.**

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Infections by salmonella species are an increasing health problem world wide.[1] In addition to causing morbidity resulting from gastrointestinal symptoms, patients can have a variety of extraintestinal complications. One of these complications is arthritis, which can be either septic or sterile (reactive). Septic arthritis is rare, but reactive arthritis is observed in 2–10% of patients with enteritis.[2] The pathogenesis of this inflammatory complication is incompletely known. Genetic factors, especially HLA-B27, play a part. In addition, in patients with reactive arthritis caused by salmonella, analogously to cases caused by *Chlamydia trachomatis*[3] or yersinia,[4] microbial antigens have been detected in the inflamed joints.[5] In contrast with yersinia arthritis,[6] according to two recent reports, there is evidence of the presence of bacterial DNA in synovial fluid of patients with reactive salmonella arthritis.[7 8] Although the triggering infections in the case of salmonella and yersinia arthritis are in both cases Gram negative bacteria and the focus of infection is in the gut, differences between the antibody profiles in the serum of patients with either of these diseases may suggest slight differences in the pathogenesis of the two forms of reactive arthritides.[9]

The duration of acute reactive arthritis varies, most patients recovering within the first three to five months. Studies on the long term prognosis of patients with Reiter's syndrome or yersinia arthritis have shown that within the subsequent 10 years, many patients present with radiological sacroiliitis. The frequency of chronic peripheral arthritis is low in yersinia arthritis but higher in Reiter's syndrome usually triggered by urethritis.[10] In contrast with studies of yersinia arthritis and Reiter's disease, the prognosis of salmonella arthritis is less well characterised. Therefore, we have evaluated the long term prognosis of patients with salmonella arthritis.

Methods

PATIENTS

The files of two hospitals were screened for patients with discharge diagnosis of salmonellosis or reactive, or postinfectious arthritis, or Reiter's syndrome. The two study hospitals were Municipal Hospital of Aurora, which

takes care of patients with infectious diseases in Helsinki, and Meilahti Hospital of Helsinki University Central Hospital, to which patients also outside Helsinki area are referred. The years covered 1974 to 1986 in Aurora and 1970 to 1986 in Meilahti.

The diagnostic criteria for reactive arthritis were as described.[11] The patients had acute asymmetric arthritis, with predilection to low extremities. Inflammatory low back pain was also accepted as a manifestation of reactive arthritis. Other causes of acute arthritis were excluded by routine tests. For salmonella infection, positive stool culture for salmonella, or serological evidence of salmonella infection (agglutinating antibody titre > 1:160), or both. Septic salmonella infections were excluded from the analysis.

There were 63 such patients. Data of the acute features of the disease were collected from the patient records. The acute clinical picture of 23 of the patients has been described previously.[11]

STUDY DESIGN

The follow up study included information about medical history with clinical examination, radiology of lumbosacral spine and sacroiliac joints (44 patients), and ultrasound of lower extremities (37 patients) to detect the presence of enthesopathy. Radiographs of lumbosacral spine and sacroiliac joints were read independently by three radiologists (AL, JK, MT) who were unaware of the clinical features of the patients. The grading of the sacroiliac joints was evaluated for both sides: 0: normal, grade I: sclerosis of ilium, grade II: sclerosis of both ilium and sacrum with irregular joint space, grade III: partial narrowing, erosions, or fusion of joint space, grade IV: bony fusion of joint space. Lumbar spine was graded as follows: grade 0: normal, grade I: squaring of the vertebral body, grade II: syndesmophytes, grade III: ankylosis of spine, bamboo spine. Ultrasound examination was performed as described previously.[12]

The presence of HLA-B27 had been studied previously in nine patients. HLA analysis of HLA-A-, B-, C-antigens (in 38 patients) and -DR antigens (in 35 patients) was performed using the standard microlymphocyte technique.

Table 1 Clinical characteristics and main laboratory findings of 63 patients during acute salmonella arthritis

	History of arthritis before salmonella		
	Yes (n=9)	No (n=54)	*Total (n=63)*
Inflamed joints, number, median (range)	4 (1–7)	4 (0–15)	4 (0–15)
Low back pain (%)	56	43	44
Arthritis of chest wall (%)	22	2	6
Heel pain (%)	11	2	3
Entesopathy (%)	22	4	6
Extra-articular symptoms (%)	44	26	29
Urethritis	44	24	27
Eye inflammation	11	13	13
Balanitis	0	3	3*
Perimyocarditis	0	2	2
ESR, mm 1st h (mean, range)	82 (12–135)	73 (3–140)	74 (3–140)
Hgb, g/l (mean, range)	124 (101–156)	128 (80–158)	128 (80–158)
WBC, 10^9/l (mean, range)	10.3 (7.1–13.4)	9.1 (3.9–17.5)	9.3 (3.9–17.5)
RF positive (%)	0	2	2†
HLA-B27 positive (%)	100	86	88‡

* Of male patients, † Of 55 patients, ‡ Of 49 patients.
ESR, erythrocyte sedimentation rate; Hgb, haemoglobin; WBC, white blood cell count; RF, rheumatoid factor.

Table 2 Antibiotic treatment and duration of acute reactive salmonella arthritis

Duration of antibiotic treatment	*Duration of arthritis (months) median (range)*
No treatment (n=25)	3.0* (1–15)
< 1 week (n=7)	3.0† (1–5)
1–4 weeks (n=13)	3.0 (2–144)
> 4 weeks (n=13)	6.0 (5–15)
Duration not known (n=13)	3.0 (0.5–6)

* Evaluable in 23 patients, † evaluable in five patients.

STATISTICAL ANALYSIS

Proportional data were compared with the χ^2 test. The Mann-Whitney U or Student's *t* tests were applied in comparisons of continuous variables.

The study was approved by the local ethical committee.

Results

ACUTE DISEASE

There were 63 patients (28 women, 35 men, mean age 36.5 years, range 18–76) with acute salmonella arthritis. Abdominal symptoms had occurred in 95% of the patients. Stool culture was positive for salmonella in 93% of the 60 patients studied, with 17 different salmonella spp detected. *S typhimurium* was the most frequent (26 cases), followed by *S enteritidis* (eight cases), and *S infantis* (five cases). One patient had positive cultures for both *S typhimurium* and *S infantis*. Twelve patients had a history of symptoms of spondyloarthropathy or acute iritis before the current acute disease (seven had had previous oligoarthritis, four had had acute iritis, and two patients had ankylosing spondylitis).

Table 1 shows the clinical characteristics and main laboratory features seen during the acute salmonella arthritis. No patient had skin symptoms or keratoderma. One patient had perimyocarditis with 2° atrioventricular conduction disturbance (Wenckebach), another patient had only minor changes in electrocardiogram.

The patients were usually treated with non-steroidal anti-inflammatory drugs. Antibiotics were prescribed to 35 of 58 patients (58%). Ten patients had received such a treatment before admission to hospital. In one of them, the antibiotic was prescribed for gastroenteritis before the appearance of joint symptoms. The use of antibiotics was not known in three cases. Sulphamethoxazole-trimethoprim combination was the most often used drug (in 20 patients).

The date of improvement could be determined for 56 patients. Median duration was three months (range 0.5 months to 12 years). In three patients, the duration was longer than 12 months. In eight patients, the joint or back symptoms ran a chronic course (see follow up). There was no trend in favour of better course of acute clinical symptoms (table 2) or late events in patients treated with antibiotics (data not shown).

Table 3 Contribution of HLA-B27 in acute salmonella arthritis

	HLA-B27+ (n=43)	*HLA-B27− (n=6)*	*p Value*
Sex (M/F)	28/15	5/1	0.0349†
Previous arthritis	7*	0	NS
Previous iritis	4	0	NS
Age, years, mean (range)	34.2 (18–76)	38.2 (21–52)	NS
Number of joints, median (range)	4.0 (1–8)	4.0 (0–7)	NS
Low back pain	24	1	NS
Urethritis	16	0	NS
Acute iritis	8	0	NS
Radiological sacroiliitis‡	2	0	NS
ESR, mm 1st h, mean (SD)	80.9 (32.6)	46.5 (27.7)	0.0180
Duration of acute arthritis§ months, median (range)	3.0 (1–144)	2.0 (0.5–5)	NS

* Numbers of patients, † Fisher's exact test, ‡ grade II–IV, § evaluable in 46 patients.

During acute arthritis, 40 patients had radiological examination of inflamed joints with radiological changes in seven patients (one with erosions in MTP joints, one with periosteal reaction, two with patchy osteoporosis, and three patients with degenerative changes only). Examination of lumbosacral spine and sacroiliac joints was performed in 26 patients (including one patient with pre-existing ankylosing spondylitis). Excluding this patient, radiology confirmed two patients (neither of them with rheumatological history) with grade II sacroiliitis.

HLA-B27 was present in 88% of the 49 patients studied. HLA-B27 was more frequent in male patients and its presence was associated with more severe inflammation and with the presence of extra-articular symptoms (table 3).

FOLLOW UP STUDY

During the subsequent years, two of 63 patients had died. The present address was not known for three patients. The remaining 58 patients were asked by mail to participate in a follow up study. Of these patients, 46 were studied at the Outpatient Department of Meilahti Hospital. Two patients living in another part of Finland were interviewed by mail. For the two patients who had died, information was collected from the hospital records. In addition, information about the later course of two patients was available from the medical records. Thus, the follow up study covered 83% of the original patient population.

Follow up time of the 50 patients extended to mean 11 years (range 5–22) after the acute arthritis. There were no significant differences between patients with and without follow up in the clinical, radiological or inflammatory variables during the acute disease or in the frequency of HLA-B27 (data not shown).

Twenty patients had recovered completely without any residual symptoms at the follow up (table 4). Ten patients complained of mild joint pains without objective synovitis, while 11 patients had experienced a new acute transient arthritis. Eight patients continued to have progressive joint or lumbosacral pains and they proceeded to have chronic spondyloarthropathy. Six of eight patients fulfilled the Rome criteria for ankylosing spondylitis.[13] One patient with initial perimyocarditis developed aortic regurgitation and severe ankylosis of the spine. Two patients died during the follow up time, one because of acute myocardial infarction, the other because of metastatic breast cancer.

Table 4 Number (%) of patients with various symptoms at follow up

	History of arthritis before salmonella		
	Yes (n=6)	*No (n=44)*	*Total (n=50)*
No residual symptoms	3 (50)	17 (34)	20 (40)
Only subjective joint pain at follow up	0 (0)	10 (23)	10 (20)
A history of inflammatory low back pain	3 (6)	19 (43)	22 (44)
Recurrent acute arthritis	3 (50)	8 (18)	11 (22)
Chronic arthritis	3 (50)	5 (11)	8 (16)
Acute iritis during follow up	1 (17)	4 (9)	5 (10)

*Table 5 Radiological examinations of patients with follow up**

	Acute disease	*Follow up*
Patients (n) with lumbosacral radiology	20	44
Radiological finding normal	18 (90)	29 (66)
Abnormal	2 (10)	15 (34)
Sacroiliitis grade I	0 (0)	9 (20)
Sacroiliitis grade II	2 (10)	2 (5)
Sacroiliitis grade III	0 (0)	2 (5)
Sacroiliitis grade IV	0 (0)	2 (5)
Lumbar spine		
Squaring	0 (0)	2 (5)
Ankylosis	0 (0)	2 (5)

* Number (%) of patients.

Radiological examination of the lumbosacral spine was performed for 42 patients. Radiology was not performed for six patients (four were not able to visit the hospital for an additional visit, two patients were interviewed by mail). In addition, latest radiographs of lumbosacral spine of the two deceased patients were available. Thus, the radiological information was available in 44 (88%) of the 50 patients in the follow up study. Twenty of 44 patients had had radiological examination also during the acute period. While two of 20 patients had had radiological evidence of radiological sacroiliitis during the acute disease, 15 of 44 patients (including one patient with pre-existing ankylosing spondylitis) had changes at the follow up examination (table 5). Grade II–IV sacroiliitis was present in six of 44 patients. The sacroiliac changes were symmetric in 11 cases and asymmetric in four cases. Male sex and high ESR during acute arthritis were predictors for sacroiliitis at the follow up (table 6).

Ultrasound of lower extremities detected 22 changes in 15 of 37 patients (41%). Bursitis near tendon insertion was observed as the only abnormality in five patients (four of them had achilles bursitis, one had bursitis at the patella region). Excluding these patients, enthesopathic changes were seen in 27% of the patients (focal changes in tendons in five, calcification in five, oedema at the tendon insertion in four, thickening of the tendon in two patients, and oedema at the insertion in one patient). Achilles insertion was the most frequent locus of enthesopathy (nine lesions) followed by insertions of the plantar fascia (four lesions) and patella tendon (three lesions). Only one patient had swelling at the greater trochanter insertion. The presence of lesions at enthesis did not correlate with the duration of acute salmonella arthritis, with the presence of peripheral or sacroiliac joint symp-

Table 6 Differences in the features of acute salmonella arthritis between patients with and without radiological sacroiliitis at the follow up study

	Sacroiliitis− (n=38)	*Sacroiliitis+ (n=6)*	*p Value*
Age, mean, years (SD)	35.5 (12.2)	36.4 (11.1)	NS
Sex (M/F)	19/19*	6/0	0.0289†
Previous arthritis, n* (%)	4 (11)	2 (33)	NS
Low back pain, n (%)	17 (45)	4 (67)	NS
Urethritis, n (%)	11 (29)	2 (33)	NS
Number of joints, median (range)	4.0 (0–7)	4.5 (1–7)	NS
Recurrent arthritis, n (%)	9 (24)	1/5 (20)	NS
ESR, median (range)	68 (3–140)	100 (70–128)	0.0435‡

* Number of patients, † Fisher's exact test, ‡ Mann-Whitney U test.

Table 7 HLA-B27 and follow up of patients (number, %) with salmonella arthritis

	HLA-B27+ (n=42)	*HLA-B27− (n=6)*	*p Value*
Asymptomatic	24/38 (63)	3/6 (50)	NS
Transient joint pains	17/38 (45)	1/6 (17)	NS
Low back pain	19/37 (51)	3/6 (17)	NS
Recurrent arthritis	9/39 (23)	0/6 (0)	NS
Chronic arthritis	8/42 (19)	0/6 (0)	NS
Iritis	5/37 (14)	0/6 (0)	NS
Radiological sacroiliitis*	6/35 (17)	0/6 (0)	NS

* Grade II–IV.

toms at the follow up study, with HLA-B27 or with sex (data not shown).

Recurrent arthritis, acute iritis, and radiological sacroiliitis were seen only in HLA-B27 positive patients (table 7). Nine patients (18%) had recurrent arthritis, in six patients associated with an infection (two patients had yersinia infection, two had enteritis, one acute respiratory infection, and one had dental focus). The frequency of HLA-DR8 was higher (40% *v* 14%; $p<0.001$ corrected for the number of DR alleles tested) and of HLA-DR2 lower (11% *v* 34%; corrected $p>0.05$) than in healthy normal Finnish blood donors. The presence of either HLA-DR4 or HLA-DR8 independently or in combination with HLA-B27 did not modify the clinical picture or the prognosis of salmonella arthritis (data not shown).

Discussion

Salmonella infections are increasing world wide. Usually such an infection leads only to minor gastrointestinal problems, but joint complications are also increasing in parallel. Septic arthritis is a rare complication, whereas reactive sterile joint complications are estimated to occur in about 2–10% of the infected patients.[2]

This study is the largest to describe the whole spectrum of acute reactive salmonella arthritis from the early features to the late prognosis. The acute clinical picture is similar to other reactive arthritides in which infection in the gut is the triggering factor.[10 14]

Most of the patients did have late symptoms, usually only transient subjective complaints without objective joint destruction. However, in 16% of the patients, the disease ran a chronic course. A few patients also experienced symptomatic or asymptomatic development of sacroiliitis. Male patients were more prone to have back problems and sacroiliitis. One of the patients even developed aortic regurgitation with spinal ankylosis. In addition to pre-existing ankylosing spondylitis, 12% of patients fulfilled the Rome criteria for ankylosing spondylitis.[13] In a previous study with similar length of follow up, we found radiological sacroiliitis in 36% of patients, half of whom had progressive changes.[15] In a similar study on yersinia arthritis by Herrlinger and Asmussen,[16] 5% of patients had developed ankylosing spondylitis, and another 5% had progression of pre-existing ankylosing spondylitis. With extended follow up, the figures may even increase. Sairanen *et al*[17] reported that of patients with shigella arthritis 20 years previously, 14% had ankylosing spondylitis and 32% had radiological sacroiliitis. During 10 year follow up, radiological sacroiliitis has been seen also in about 30% of patients with Reiter's disease, usually triggered by urethritis.[18]

Enthesopathy is a feature associated with spondyloarthropathy.[19] Ultrasound examination has proved to be a sensitive method to study objectively the presence and nature of enthesitis. During active spondyloarthropathy, we have previously seen enthesopathy in 67% of the patients.[12] In contrast with a good clinical course of arthritis, the ultrasound findings persisted in most of the patients during a follow up of six months.[20] This study shows that enthesopathy is a long term feature in spondyloarthropathy, because about one quarter of the patients had such lesions a mean of 11 years after the acute episode. The findings were more of long term nature, because calcifications and focal intratendinous changes were more frequently seen than in acute disease.[12] However, the frequent finding of oedema at the insertion refers to the presence of active inflammation in these patients.

Despite the constant genetic background, it is interesting that most patients did not have recurrent acute arthritis. This is in accordance with our previous results on patients with yersinia arthritis.[15] In contrast with this, patients with Reiter's syndrome triggered by urogenital infection seem to be more vulnerable to recurrent urethritides and consequently recurrent episodes of arthritides. This might be one reason for the worse prognosis of such patients.[10]

Our patients were selected from series of hospitalised patients. It is interesting therefore to compare our results with those from single source epidemics.[21–26] In contrast with the high frequency of HLA-B27 in this study, we observed a low frequency in a population study on subjects with postinfectious joint symptoms after an outbreak of salmonella infection in Finland.[23] Thompson *et al*[24] have recently described the five year prognosis of patients from a cohort infected with *S typhimurium*. Though the patients also had low frequency of HLA-B27, two thirds of the patients continued to have subjective complaints, a few of them with considerable peripheral symptoms. Radiological findings of the spine were not reported, but about 60% of their patients had axial symptoms.

The treatment of reactive arthritis is still unresolved. In this study, 58% of the patients had received antibiotic treatment for various length of time, the decision left to the clinician. According to the results, patients with more prolonged disease seemed to have been treated

for longer duration. However, no obvious benefit was seen with respect to the duration of acute arthritis. For *Chlamydia trachomatis* infection, the existing evidence speaks in favour of early antibiotic treatment as a preventive against arthritic complications[25] and prolonged antibiotic treatment in the case of acute arthritis.[26] For the optimal treatment of reactive arthritis triggered by salmonella or other enteric pathogens, we have to wait for the results of the ongoing placebo controlled studies.

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